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Dichotomous Roles of TGF- β in Human Cancer

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Abstract

Transforming growth factor- β (TGF- β) mediates/regulates numerous biological processes including embryonic development and maintenance of cellular homeostasis in a context dependent manner. Consistent with its central role in maintaining cellular homeostasis, inhibition of TGF- β signaling results in disruption of normal homeostatic processes and subsequent carcinogenesis, defining the TGF- β signaling pathway as a tumor suppressor. However, once carcinogenesis is initiated, the TGF- β signaling pathway functions to promote cancer progression. This dichotomous function of the TGF- β signaling pathway is mediated both through altered effects on the cancer cells, including via inducing epithelial to mesenchymal transition, as well as through effects on the tumor microenvironment, including via effects on angiogenesis and immunosurveillance. Current studies support inhibition of TGF- β signaling either alone, or in conjunction with anti-angiogenic therapy or immunotherapy as a promising strategy for the treatment of human cancers.

Transforming growth factor- β (TGF- β) is a ubiquitously-expressed cytokine that mediates or regulates a wide spectrum of biological processes including embryonic development, maintenance of cellular homeostasis, angiogenesis and immune regulation in a context dependent manner. Consistent with its pervasive and central role in maintaining cellular homeostasis, inhibition of TGF- β signaling results in disruption of normal homeostatic processes and subsequent carcinogenesis, defining the TGF- β signaling pathway as a tumor suppressor. However, once carcinogenesis is initiated, the TGF- β signaling pathway functions to promote cancer progression (Figure 1). This dichotomous function of the TGF- β signaling pathway during cancer initiation and progression presents a tremendous challenge, both in terms of understanding how the same pathway mediates these divergent effects, and in confounding efforts to target this pathway for therapeutic purposes. Here we review potential mechanisms through which TGF- β mediates its dichotomous functions during cancer progression and establish a framework for rationale targeting of the pathway in human patients.

Mechanism of TGF- β Signaling

TGF- β initiates downstream signaling when the dimerized TGF- β ligand binds to the type III TGF- β receptor (T β RIII), which then presents ligand to the type II TGF- β receptor (T β RII) [1, 2]. T β RII then recruits and phosphorylates the type I TGF- β receptor (T β RI) to active its kinase activity [3, 4]. In canonical TGF- β signaling, activated T β RI phosphorylates the intracellular proteins Smad2 or Smad3, which then complex with Smad4 before translocating into and accumulating in the nucleus where they act with co-activators or co-repressors to initiate transcriptional changes [5–8]. TGF- β can also signal through non-canonical pathways including p38, JNK, Erk1/2 and PI3K [9] and has also been reported to signal through Smad1/5/8 [10, 11]. The TGF- β signaling pathway is regulated at many levels. At the extracellular level, TGF- β ligand bioactivity is regulated by activation steps, which release it from a latent complex [12], as well as by interaction with antagonists, including the soluble type III TGF- β receptor [13, 14]. At the intracellular level, negative feedback is provided both by the inhibitory Smad6 and Smad7, which are upregulated by TGF- β and antagonize signaling at the receptor/Smad level [15–17], and by transcriptional repressors, including Ski and SnoN, which are upregulated by TGF- β and antagonize signaling at the Smad/promoter level [18]. Perturbations to TGF- β signaling can occur at each of these multiple levels of regulation, including increased ligand availability due to loss of shed T β RIII [13, 14], loss or mutation of cell surface receptors [19–25] or of downstream mediators [26–30].

TGF- β as a Tumor Suppressor

Dysregulation of TGF- β signaling pathway is a frequent event in human cancers. Disruption can occur either through deletion or inactivating mutations of the TGF- β receptors or their downstream effectors. T β RII deletions or mutations are often seen in colon, gastric, bladder and ovarian cancers [19–23], and T β RI receptor alterations are also commonly seen in ovarian, head and neck, breast, bladder, and prostate cancers, among others [21, 23–25]. Over 50% of pancreatic cancers and 15% of colon cancers harbor alterations to the downstream effector Smad4 [26–28]. Additionally, Smad4 mutations are a known cause juvenile polyposis, an inherited autosomal dominant disease that predisposes patients to hamartomatous polyp formation and colorectal cancer [29]. Other mediators of TGF- β signal transduction, including Smad2 and Smad3, are mutated in colorectal cancer [28], hepatocellular carcinoma [31] and gastric cancer [30]. Contrary to the loss of function of TGF- β mediators, antagonists of the TGF- β pathway including Smad7, Ski, and SnoN are often overexpressed in colorectal cancer, melanoma and breast cancer, among others [32–36]. The tumor suppressive role of TGF- β is largely thought to be due to TGF- β 's roles in limiting proliferation, promoting apoptosis and inducing senescence in normal cells.

Tumor Suppressive Role of TGF- β in proliferation

In normal epithelial and hematopoietic cells, TGF- β inhibits cell growth by targeting cell-dependent kinases (CDKs) and their inhibitors (CDK-Is) that are responsible for controlling progression past the G1 phase of the cell cycle during proliferation. TGF- β promotes the expression of the CDK-Is p15^{INK4B}, p21^{CIP1} and p27^{KIP1}, which inhibit cyclin-CDK

complexes, leading to G1 phase cell cycle arrest [37–40]. In addition, TGF- β inhibits CDK4, which is required for exit from the G1 phase and progression into the S phase of the cell cycle, directly mediating growth suppression. [41, 42]. TGF- β also suppresses c-Myc, leading to suppression of p15^{INK4B} and p21^{CIP1}, and thus, loss of cell proliferation [43–45]. Id family proteins including Id1, Id2 and Id3, which help mediate differentiation and cytostasis, are also repressed by TGF- β , resulting in decreased proliferation [46, 47].

When TGF- β signaling is disrupted by mutation, deletion or altered expression of critical components, this anti-proliferative signaling is lost, leading to sustained proliferation due to lack of G1 cell cycle arrest. The critical role for loss of TGF- β signaling in mediating sustained proliferation in human cancers is supported by the ability of restoration of TGF- β signaling to rescue TGF- β responsiveness and control of proliferative signaling. Thus, restoration of T β RII in the human breast cancer cell line, MCF-7, or of Smad3 in the gastric cancer cell line, SNU-484, rescues TGF- β sensitivity while TGF- β stimulation once again initiates growth arrest [30, 48]. In a reciprocal manner, loss of negative regulators of TGF- β signaling, including SnoN and SKI, can inhibit proliferation of breast, lung and pancreatic cancer cells [49, 50].

Tumor Suppressive Role of TGF- β in apoptosis

TGF- β triggers apoptosis in a wide range of cell types acting through both Smad-dependent and independent pathways. The Smad-dependent pathway involves the induction of pro-apoptotic proteins including TGF- β inducible early response gene (TIEG1) [51], death-associated protein kinase (DAPK) [52, 53], and inositol-5-phosphatase (SHIP) [53]. TIEG1 induces oxidative stress [54] while DAPK induces mitochondrial cytochrome c release to trigger apoptosis [52]. SHIP inhibits the pro-survival PI3K-Akt pathway to instigate cell death [53]. TGF- β also works through Smad4 to induce SAPK/JNK pathway signaling to induce the expression of pro-apoptotic genes including BIM, BCL-2, and BAX and caspase 9 [55–57]. Independent of the SAPK/JNK pathway, TGF- β can also promote the expression of pro-apoptotic genes, including BIK and caspase 3 and 8, while suppressing anti-apoptotic genes, including Bcl-X_L, XIAP, and Bcl-2 [58–61]. TGF- β is also linked to the Fas-mediated apoptosis pathway through DAXX, an adaptor protein that mediates Fas receptor signaling. DAXX stabilizes T β RII, leading to JNK activation and potentiation of Fas apoptosis signaling [62]. Interestingly, cells that are resistant to TGF- β induced growth inhibition can still respond to TGF- β induced apoptosis through inducing the translocation of the mitochondrial protein ARTS to the nucleus. This translocation then stimulates caspase 3 activation and suppresses the anti-apoptotic proteins Bcl-X_L and XIAP to induce apoptosis [63–65]. Apoptosis can also be induced after malignant epithelial-to-mesenchymal transition (EMT) if cells are TGF- β responsive. In Smad4-expressing TGF- β responsive pancreatic cancer, TGF- β can stimulate cells to undergo EMT while simultaneously suppressing Klf5 signaling. Without Klf5 cooperation, Sox4 induces apoptosis [66].

These TGF- β -induced apoptotic homeostatic mechanisms are also disrupted when intact TGF- β signaling is lost. In many cases, TGF- β 's apoptotic signaling is Smad dependent, with overexpression of Smad4 inducing apoptosis in MDA-MB-468 breast cancer cells [67]. Meanwhile, use of a dominant-negative Smad3 prevented apoptosis in the Hep3B

hepatocarcinoma cell line [68]. T β RII's role in mediating apoptosis is also critical for regenerating epithelial tissue, where apoptosis helps prevent hyperproliferation. When T β RII is lost in skin epithelial cells, the loss of apoptosis disrupts this balance between apoptosis and hyperproliferation, leading to oncogenic progression and invasive squamous cell carcinoma [69]. Similarly, knock-down of Smad2 or expression of a dominant negative T β RII in NRP-152 cells, a non-tumorigenic prostate epithelial cell line, greatly reduced sensitivity to TGF- β -induced apoptosis, subsequently leading to malignant transformation and the newfound ability to form tumors when injected into nude mice [70, 71]. On the other hand, in TGF- β non-responsive Smad4 null pancreatic cancer cells, Klf5 signaling is induced, inhibiting apoptosis, leading to cell immortalization and subsequent tumorigenesis [66].

TGF- β as a Tumor Promoter

While TGF- β may suppress cancer initiation, in cancers that do form, increased expression of TGF- β ligands has been broadly reported, including in breast [72, 73], esophageal [74], colorectal [75], gastric [76], lung [77] and pancreatic cancers [78]. In these cancers, increases in TGF- β ligand levels have been demonstrated both locally and systemically, with elevated circulating levels. Higher levels of TGF- β have been demonstrated in lymph node metastasis compared to primary tumors or in tumors that eventually metastasize. High levels of TGF- β also correlate with increased invasiveness, disease progression and a poorer prognosis [72, 75–80]. TGF- β can be produced by the tumor cell itself or other cells in the tumor microenvironment including stromal cells, macrophages and platelets [81–83]. Additionally, secreted TGF- β that is stored in the extracellular matrix can be released by the tumor-associated increase in matrix degradation factors [84–86]. Although the increase in TGF- β may enhance the cell autonomous tumor suppressive effects, many tumorigenic cells have already lost their TGF- β responsiveness and thus, its homeostatic effects. Instead, this increase in TGF- β may act in the tumor microenvironment to promote changes that encourage tumor progression. Along those lines, TGF- β has roles in promoting angiogenesis, inducing EMT, modifying the extracellular matrix, and suppressing immune surveillance.

Tumor Promoter Role of TGF- β in EMT and Metastasis

TGF- β induces EMT during normal growth and development. It is essential for embryonic tissue differentiation [87] and normal heart and lung development [88, 89]. EMT is also accompanied by changes in tight junction and cell adhesion molecules, including decreasing E-cadherin, claudin and occludin expression while upregulating vimentin and N-cadherin [90, 91]. The EMT gene signature involves the Smad-mediated induction of HMGA2 to mediate Snail, Slug, ZEB2 and Twist expression [92] as well as the Smad-independent upregulation of the polarity protein Par6 [93] which lead to loss of cell polarity, E-cadherin downregulation and increased invasion and metastasis [94]. TGF- β also induces cytoskeleton re-organization by inducing focal adhesion kinase signaling, smooth muscle actin expression and stress fiber formation [95]. These EMT-associated changes allow cells to change to lose connections to other epithelial cells, acquire a fibroblast phenotype and migrate away from their initial location. This EMT process can be hijacked by cancer cells

to lead to decrease cell adhesion and encourage migration and invasion to promote to cancer metastasis.

TGF- β signaling is essential to EMT in cancer cells. In squamous cell carcinoma and breast cancer, use of a dominant negative T β RII abrogated their ability to undergo EMT and migration and metastasize to distant sites [96–98]. Meanwhile, restoration of T β RII activity in the typically T β RII-null and non-invasive hereditary nonpolyposis colorectal cancer cells promoted invasive behavior [99]. Transgenic mice with activated TGF- β 1 expression in keratinocytes demonstrated an increased propensity to form spindle cell carcinomas, suggesting that TGF- β 1 is involved in this keratinocyte-to-spindle cell transition [100]. In breast cancer, TGF- β also has been demonstrated to induce MDM2, destabilizing p53, leading to EMT and tumor progression [101]. In addition, in cancers where p53 is mutated, TGF- β induces the formation of a mutant p53, Smad and p63 complex. In this complex, p63 loses its tumor suppressive function, allowing both TGF- β and mutant p53 to initiate EMT and metastasis [102]. Moreover, high levels of TGF- β are often seen at the invasive front, suggesting that TGF- β is involved in the EMT, migration and invasion of tumor cells [96].

TGF- β can also increase migration, invasion and the metastasis of cancer cells, including mediating the balance between single-cell versus group migration of cancer cells. In TGF- β responsive breast cancer cells, single cell migration occurs through a Smad-mediated pathway involving downstream activation of EGFR, Jun and Rho signaling pathways and CTGF. However, collective migratory behavior and increased lymph node metastasis is seen in when TGF- β signaling is inhibited [103]. TGF- β has been demonstrated to promote migration in prostate cancer by inducing cytoskeletal rearrangement in a Cdc42 and RhoA dependent fashion, increasing formation of stress fibers and lamellipodia [104] while TGF- β -mediated induction of DOCK4 in lung cancer also leads to increased cell protrusion, motility and metastasis [105]. Breast cancer migration and invasion can also be inhibited by ectodomain shedding of T β RIII, which generates a soluble form of the receptor that can act as a ligand sink. Abrogation of soluble receptor generation increases migration and invasion [14]. Meanwhile, the cytoplasmic domain of T β RIII signals through GIPC to suppress cancer progression and loss of the receptor increases migratory and invasive behavior [106]. TGF- β is also able to down-regulate tumor-suppressive microRNAs that including miR-124 and miR-187, enhancing EMT and metastasis. miR-124 also contributes to a positive feedback loop that further upregulates TGF- β expression leading increased metastasis [107, 108].

In addition to promoting EMT and metastasis, TGF- β can also promote colonization of metastatic cells through mesenchymal-to-epithelial transition (MET) and upregulation of metastatic niche genes. TGF- β promotes MET in breast cancer cells that metastasize to the lung through an Id1-Twist1 signaling axis, leading to lung colonization [109]. Furthermore, TGF- β is critical for the establishment of bone metastasis in breast cancer by inducing growth factors, including PTHrP, RANKL, IL-11 and CTGF, which encourage bone colonization [98, 110–112]. TGF- β is also released from the bone itself, further promoting bone metastasis, bone destruction, muscle weakness and loss of muscle mass [113].

Tumor Promoter Role of TGF- β in the Tumor Microenvironment

The stroma in the tumor microenvironment consists of many cells and structures that are important for normal tissue physiology but also can influence tumor progression. These cells and structures include myofibroblasts, blood vessels and immune cells which reside in the extracellular matrix (ECM), which is comprised of collagen, elastin, fibronectin and laminin scaffolding proteins [114]. Together with its cell autonomous effects, TGF- β can influence these complex stromal components to support tumor growth and progression.

Tumor Promoter Role of TGF- β on the Extracellular Matrix

Differentiation of fibroblasts, stellate cells or smooth muscle cells into myofibroblasts occurs normally in response to tissue injury and TGF- β , and these myofibroblasts secrete extracellular matrix (ECM) components and help remodel the ECM to aid with wound healing. Once repair is completed, they undergo apoptosis, suggesting that myofibroblasts are a transient rather than permanent cell population [115]. In cancer, TGF- β helps differentiate fibroblast into myofibroblasts, which then become a persistent and important component of the tumor microenvironment, where they secrete pro-tumor growth factors [116–118]. This progression from fibroblastic to myofibroblastic characteristics correlates with tumor progression in colon and breast cancer [119, 120]. Myofibroblasts also acquire autocrine and paracrine signaling that promote a pro-tumorigenic phenotype by stimulating the expression of proteins including MMPs, cytokines and chemokines to promote proliferation, EMT, invasion and angiogenesis. These proteins lead to further increase in TGF- β levels and also stimulate tumor cells to further promote progression [116, 121–124]. Loss of TGF- β signal by deletion of T β RII in fibroblasts resulted in prostate and gastric cancer due to the dysregulation of HGF, MST1 and TGF- α in surrounding tissue, further suggesting that fibroblasts are involved in both autocrine and paracrine signaling in the tumor microenvironment. Further, co-injecting T β RII null fibroblasts with renal cell carcinoma cells promoted tumor invasion, angiogenesis and proliferation [121, 122]. Stromal TGF- β signaling also helped establish a metastatic niche for colorectal cancer cells, promoting colonization, while use of a T β RI inhibitor prevented metastasis. A TGF- β induced gene signature in fibroblasts is also predictive of disease recurrence while low stromal signaling correlated with improved survival [125].

TGF- β is also involved in ECM remodeling through increasing the expression of matrix metalloproteinases (MMPs), including MMP1, MMP2, MMP7, MMP9, MMP13 and MMP14. These MMPs degrade the ECM, providing a pathway for tumor migration and invasion and activates the TGF- β sequestered in the ECM, feeding a positive feedback loop. ECM remodeling also stimulates angiogenesis, further supporting tumor growth [126, 127]. Meanwhile, MMP13 induced by TGF- β promoted tumor extravasation from the tumor microenvironment to support metastatic growth [128, 129]. Changing the ECM force mechanics also influence tumor progression: decreasing the ECM rigidity increased the sensitivity of cells to TGF- β -induced apoptosis while increasing rigidity promoted TGF- β -mediated EMT [130].

Tumor Promoter Role of TGF- β in Angiogenesis

Endothelial cells are the major cell type regulated during angiogenesis and exhibit increased permeability, proliferation, migration and invasion during the formation of new blood vessels [131]. The TGF- β signaling pathway has an important role in endothelial biology and normal angiogenesis. Mice deficient in TGF- β signaling in endothelial cells due to the loss of ALK-1, a type I TGF- β receptor [132]; T β RII [133, 134]; endoglin, a TGF- β co-receptor [135, 136]; or TGF- β 1 [137] exhibit dysregulated angiogenesis and embryonic lethality [132, 135, 136]. TGF- β also induces the production pro-angiogenic growth factors, including VEGF and CTGF by epithelial cells and fibroblasts [138, 139] and directly stimulates endothelial cells to form capillaries. Meanwhile, TGF- β -induced VEGF and CTGF induces endothelial migration that is necessary for angiogenesis [133, 140].

During tumor growth the tumor quickly outgrows the existing vasculature and induces angiogenesis to provide nutrients and oxygen to the cancer cells [141]. TGF- β has an important role for inducing and sustaining tumor angiogenesis, which in turn supports cancer progression and metastasis. Higher levels of TGF- β in the tumor microenvironment correlates with increased vascular density, tumor progression and worse prognosis in a non-small cell lung cancer cohort [77]. High circulating levels of TGF- β 1 in plasma also correlated with increased tumor angiogenesis and poor prognosis in prostate cancer, renal cell carcinoma and hepatocellular carcinoma [80, 142–144]. TGF- β can also induce the endothelial microRNA miR-29a, leading to PTEN/AKT pathway activation and increased angiogenesis [145]. In xenografts, Chinese hamster ovary cells transfected to overexpress TGF- β 1 resulted in increased angiogenesis while a TGF- β neutralizing antibody inhibited angiogenesis, further demonstrating the importance of TGF- β in angiogenesis and tumor progression [146]. In addition to TGF- β ligand effects, TGF- β receptors are also critical for angiogenesis. Treating mice xenografted with T β RII null 786-O renal carcinoma cells with a TGF- β neutralizing antibody also decreased angiogenesis [147]. Endoglin also works in concert with VEGF to induce tumor angiogenesis. Suppression of both endoglin and VEGF led to decreased endothelial tube formation and subsequent angiogenesis [148, 149].

TGF- β can also generate an environment more conducive to endothelial cell migration, which is essential for angiogenesis, by inducing MMP activity to modify the ECM. TGF- β can act through one of its type I receptors, ALK5, to enhance MMP9 expression, and promote the formation of new blood vessels. Use of dominant negative ALK5 or knock-down of MMP9 enhanced angiogenesis and tumor progression in breast and prostate cancer cell lines [150, 151].

Tumor Promoter Role of TGF- β in Immune Surveillance

TGF- β is generally immunosuppressive and exerts these suppressive effects on all the components of the immune system. It suppresses the activity of cytotoxic T-cells, natural killer cells and dendritic cells and creates a pro-inflammatory environment, which recruits macrophages and neutrophils. These effectors secrete tumor promoting cytokines and chemokines including TGF- β , initiating a positive feedback loop that further promotes tumor progression [152, 153]. Since TGF- β is often upregulated in the tumor

microenvironment, tumors are able to evade immune destruction through both immunosuppression and decreased immune surveillance.

Cytotoxic CD8⁺ T-cells can produce cytokines including perforins, granzymes and IFN- γ to induce apoptosis of any cancer cell that they encounter. However, TGF- β can inhibit their activity through transcriptional repression of these mediators by Smads and ATF1. Moreover, preventing TGF- β signaling through generating cytotoxic T-cells that express dominant-negative T β RII restored the cytotoxic T-cell activity and prolonged survival [154]. In addition to suppressing cytotoxic T-cell activity, TGF- β can also induce regulatory T-cell (Treg) differentiation [155, 156], leading to immunosuppression and loss of immune surveillance. Tregs then respond to TGF- β by preventing cytotoxic CD8⁺ T-cell proliferation and induction, inhibiting the release of cytotoxic cytokines and chemokines and further dampening anti-tumor immune responses [157].

Natural killer (NK) cells also play an important role in immune surveillance by recognizing tumor cells and initiating a cytotoxic response [158]. TGF- β can suppress NK cell activation by inhibiting IL-15 production and downregulating its activating receptor NKG2D [159, 160]. In addition, TGF- β also can induce miR-183 expression to destabilize DAP12, a receptor that is required for NK cell cytotoxicity [161]. Treating NK cells with TGF- β decreased their ability to release cytokines including perforin to induce tumor cell apoptosis while TGF- β neutralizing antibodies reversed this phenotype by promoting IL-15 production and NKG2D and DAP12 expression, which promoted NK cell survival and activation and allowed them to regain their effector function [159–161].

Dendritic cells (DC) are antigen presenting cells that are responsible for inducing the adaptive T-cell response and their activity is important for anti-tumor immunity [162, 163]. TGF- β prevents the differentiation of DCs from myeloid precursors and instead shifts differentiation toward the anti-tumorigenic myeloid-derived suppressor cells through the upregulation of the TGF- β responsive gene ID1 [164]. Specifically deleting T β RII in myeloid cells to abolish TGF- β signaling in dendritic cells increased their ability to activate T-cells, leading to decreased tumor growth. On the other hand, treating myeloid precursor cells with TGF- β inhibited their ability to activate T cells [165]. In addition, TGF- β inhibition alone has been shown to subdue DC-mediated Treg activation, and when combined with anti-CTLA-4 immunotherapy, synergistically decreased melanoma growth and metastasis though neither alone prevented progression [166].

TGF- β has been shown to drive polarization of neutrophils from an anti-tumor phenotype (N1) to a tumorigenic phenotype (N2). In the presence of TGF- β , neutrophils develop into a pro-tumorigenic phenotype and showed a decreased ability to activate cytotoxic T-cells and secrete anti-tumorigenic cytokines and chemokines. Furthermore, depletion of these neutrophils lead to a decrease in tumor size. However, treating mice with SM16, an Alk4/Alk5 T β RI kinase inhibitor, allowed tumor suppressive neutrophils to hone to the tumor, leading to cytotoxic T-cells activation and secretion of cytokines and chemokines to promote immune surveillance. When these neutrophils were then systemically depleted, tumors exhibited rapid growth, suggesting that without TGF- β stimulation, neutrophils retain their tumor suppressive phenotype [167].

Macrophages can also be divided into two groups, with the classically activated M1 phenotype regarded as tumor suppressive and the alternatively activated M2 phenotype as tumor promoting. TGF- β is a critical driver for macrophages adopting the M2 phenotype [168], which produce cytokines and chemokines including MMP9, CXCL8, CXCL12, VEGF, and IL-10 that induce tumor growth and invasion, modify the ECM and promote angiogenesis. Moreover, macrophages also suppress the adaptive arm of the immune system, further preventing immune responses [169].

Conclusion

Though much work has been done on TGF- β 's role as a tumor suppressor and tumor promoter, the mechanism by which this switch occurs has yet to be elucidated (Figure 1). As with most aspects of tumor progression, there are likely to be multiple mechanisms for this switch, including both cell autonomous (i.e. EMT) and non-cell autonomous (i.e. angiogenesis, immune system) mechanisms. Recent studies support the involvement of 14-3-3 ζ , which is able to simultaneously induce cytostasis by downregulating 14-3-3 σ , p53 and p21^{CIP1} and promote bone metastasis by upregulating PTHrP and other bone metastasis gene signatures [170], as well as the anti-oxidative stress transcription factor Nrf2 [171–173].

Early trials using TGF- β inhibitors have demonstrated that they can promote anti-tumorigenic effects even in Smad4 defective tumors, suggesting that they may function to inhibit TGF- β function in the tumor microenvironment, including angiogenesis and immune surveillance [174]. Indeed, agents targeting endoglin (e.g. TRC-105) and ALK1 (e.g. ACE-041, PF-03446962) have demonstrated single agent efficacy in Phase I studies [175–177]. In addition, with the emerging role of immunotherapy in cancer treatment and the effects of TGF- β on inhibiting the immune system, combination of TGF- β inhibition with immunotherapy appears promising. Supporting this premise, in the context of breast cancer, TGF- β inhibition was able to increase the effectiveness of a HER2 vaccine [178], and in the context of melanoma, TGF- β inhibition restored sensitivity to anti-CTLA-4 therapy [166]. Better understanding of the influence of TGF- β on the different components of the tumor microenvironment will be critical to fully harnessing anti-TGF- β targeted therapy and rational combinations with other targeted approaches.

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Figure 1.

TGF- β has cell autonomous roles as a tumor suppressor and promoter by controlling proliferation, apoptosis and EMT, as well as non-cell autonomous tumor promoting roles in the microenvironment by remodeling the extracellular matrix, inducing angiogenesis and suppressing immune surveillance.

Abbreviations: CDK-I (cell-dependent kinase inhibitors), CDKs (cell-dependent kinases), T β RI (type I TGF- β), T β RII (type II TGF- β receptor), T β RIII (type III TGF- β receptor), MMPs (matrix metalloproteinases), Tregs (regulatory T cells), MDSCs (myeloid-derived suppressor cells), NK cells (natural killer cells), DCs (dendritic cells)